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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/519,110	02/03/2006	Rene Etcheberrigaray	17357.01001US	9509

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EXAMINER	
WANG, SHENGJUN	
ART UNIT	PAPER NUMBER
1627	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/519,110	ETCHEBERRIGARAY ET AL.	
	Examiner	Art Unit	
	Shengjun Wang	1627	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 November 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *37-47,49,50,52-63,65,66,68-79,81,82 and 84* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *37-47,49,50,52-63,65,66,68-79,81,82 and 84* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *10/22/2009*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. The terminal disclaimer filed on November 23, 2009 disclaiming the terminal portion of any patent granted on this application which would extend beyond the expiration date of US 6,825,229 has been reviewed and is accepted. The terminal disclaimer has been recorded.

2. Receipt of applicants' amendments and remarks submitted November 23, 2009 is acknowledged.

Double Patenting Rejections

3. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

4. Claims 37-84 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 12-67 of copending Application No. 11/802842. Although the conflicting claims are not identical, they are not patentably distinct from each other because The claims in '824 are directed to a method of treating cognitive disorders, particularly Alzheimer's disease, comprising administering to the' patient a

composition comprising PKC activator, particularly bryostatin compound. As to the functional limitation "decrease soluble Aβ" note, . intended function of a method is not seen to carrier patentable weight if the method is obvious. Furthermore, The instant claims are directed to affecting a biochemical pathway with an old and well known subject matter. The argument that such claims are not directed to the old and well known ultimate utility (activating PKC and thereby treating Alzheimer's disease) for the compounds, e.g., bryostatin, are not probative. It is well settled patent law that mode of action elucidation does not impart patentable moment to otherwise old and obvious subject matter. Applicant's attention is directed to In re Swinehart, (169 USPQ 226 at 229) where the Court of Customs and Patent Appeals stated "is elementary that the mere recitation of a newly discovered function or property, inherently possessed by thing in the prior art, does not cause a claim drawn to those things to distinguish over the prior art." the claims are directed to the ultimate utility set forth in the prior art, albeit distanced by various biochemical intermediates. The ultimate utility for the claimed compounds is old and well known rendering the claimed subject matter either anticipated, or obvious to the skilled artisan.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claim Rejections 35 U.S.C. 112

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 37-84 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the macrocyclic lactones of bryostatins, and neristatins does not

reasonably provide enablement for any other macrocyclic lactone. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

7. The instant specification fails to provide information that would allow the skilled artisan to practice the instant invention without undue experimentation. Attention is directed to In re Wands, 8 USPQ 2d 1400 (CAFC 1988) at 1404 where the court set forth the eight factor to consider when assessing if a disclosure would have required undue experimentation. The court recited eight factors:

1) the quantity of experimentation necessary,

2) the amount of direction or guidance provided,

3) the presence of absence of working examples,

4) the nature of the invention,

5) the state of the prior art,

6) the relative skill of those in the art,

7) the predictability of the art, and

8) the breadth of the claims.

The claim recites the employment of any macrocyclic lactone for decrease of soluble Aβ-40. The application disclosed the association of PKC and Alzheimer's diseases and soluble Aβ. The application also discloses that bryostatin compounds, known PKC activators, are useful for decreasing soluble Aβ-40. See, particularly, the drawing. There are many other kinds of macrocyclic lactones and their biological properties have not been fully explored, such as those disclosed by Hodge et al. (US 3,503,994). The application fails to provide any working

examples, guidance and direction beyond the particular PKC activators herein. Applicants fail to provide information allowing skilled artisan to ascertain any other macrocyclic compounds for the utility herein claimed without undue experimentation. The pharmaceutical art is unpredictable, requiring each embodiment to be individually assessed of physiological activity. The instant claims read on all macrocyclic lactone, necessitating an exhaustive search for the embodiments suitable to practice the claimed invention, absent undue experimentation.

Claim Rejections 35 U.S.C. 112

8. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

9. Claims 40, 42, 55-58 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

10. Claims 40, 42, 55-58 recite the limitation "benzolactam, the pyrrolidinone". There is insufficient antecedent basis for this limitation in the claim.

Claims Rejections 35 U.S.C. 103

11. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

12. Claims 37-47,49,50,52-63,65,66,68-79,81,82 and 84 are rejected under 35 U.S.C. 103(a) as being unpatentable over Choi et al. (JP 2001240581, IDS), or Tamura et al. (JP 06279311, IDS) in view of Zhang et al. (IDS), and Driedger et al. (US 6,043,270, IDS).

13. Choi et al. teaches that PKC activators are particularly useful for treating CNS disorders, dementia or Alzheimer's disease. See, particularly paragraphs [0001-0003] and [0132]of the English translation attached herein. Tamura et al. teaches PKC activators are useful for treating senile dementia accompanied central nerve disorders, such as Alzheimer's disease. See, particularly, See, particularly paragraphs [0001] and [0002]of the English translation attached herein.

14. The primary references do not teach expressly the employment of bryostatin 1 for treating Alzheimer's disease or other CNS disorders herein claimed.

15. However, Zhang et al. teaches that bryostatin 1 is a known PKC activator. See, particularly, the abstract. Driedger et al. teaches various known PKC activators, including bryostatin type. See, particularly, col. 9-10; col. 18, lines 10-43. Driedger et al also teaches that the PCK activators are useful for improving central nervous system functions such as memory and learning, particularly for Alzheimer's diseases. The PKC activator may be employed for treating human and veterinary disease. See, col. 48, line 22-55.

Therefore, it would have been prima facie obvious to a person of ordinary skill in the art, at the time the claimed the invention was made, to employ bryostatin 1 as the PKC activator for treating CNS disorders, such as Alzheimer's disease, brain damage, both in human and in animals.

16. A person of ordinary skill in the art would have been motivated to a person of ordinary skill in the art, at the time the claimed the invention was made, to employ bryostatin 1 as the PKC activator for treating CNS disorders, such as Alzheimer's disease, brain damage by stroke because bryostatin 1 is a known PKC activator, and bryostatin type PKC activators are particularly known for useful for treating CNS disorders both for human and animals. As to the particularly mechanism limitation such as for "decrease soluble Aβ", note intended function of a method is not see to carrier patentable weight if the method are obvious. Furthermore, The instant claims are directed to affecting a biochemical pathway with an old and well known subject matter. The argument that such claims are not directed to the old and well known ultimate utility (activating PKC and thereby treating Alzheimer's disease) for the compounds, e.g., bryostatin, are not probative. It is well settled patent law that mode of action elucidation does not impart patentable moment to otherwise old and obvious subject matter. Applicant's attention is directed to In re Swinehart, (169 USPQ 226 at 229) where the Court of Customs and Patent Appeals stated "is elementary that the mere recitation of a newly discovered function or property, inherently possessed by thing in the prior art, does not cause a claim drawn to those things to distinguish over the prior art." the claims are directed to the ultimate utility set forth in the prior art, albeit distanced by various biochemical intermediates. The ultimate utility for the claimed compounds is old and well known rendering the claimed subject matter obvious to the skilled artisan. It would follow therefore that the instant claims are properly rejected under 35 USC 103.

Response to the Arguments

Applicants' amendments and remarks submitted November 23, 2009 have been fully considered, but are not persuasive with respect to the rejections set forth above.

Applicants contend that the claimed invention is enabled to its full scope, particularly, for "macrocyclic lactone" as the application provides detailed method for high throughput screening for those compounds. Applicants further argue that the scope is narrow as it requires the compound be PKC activator. Applicants finally assert that the search of those macrocyclic lactone suitable for claimed invention is mere a routine experimentation. The arguments are not persuasive. Particularly, the scope of the compounds encompasses any macrocyclic lactones that may have the PKC activate property; and guidance is very limited, the only structural information of the compounds is "macrocyclic lactone". As discussed in the rejections, many structurally distinct compounds share this common structural feature. See, for example, the compounds disclosed Hodge et al. (US 3,503,994). The other limitations of the compounds: "PKC activator" and capability to decrease soluble Aβ-40 are functional. The application, no the prior art, provides no guidance and direction as to the structural-activity relationship. The search and identification of these compounds are solely based on the screening method as described in the application. The screening method is no more than a hunting tool for the compounds suitable for the claimed method. As it is well-settled that "… a patent is not a hunting license. It is not a reward for the search, but compensation for its successful conclusion. '[A] patent system must be related to the world of commerce rather than to the realm of philosophy".

See Brenner v. Manson, 833 O.G. 1349, 148 USPQ 689, 696:

Further, the art of finding a chemical compound that inhibits or binding to a particular site is very unpredictable. See University of Rochester v. G.D. Searle &Co. 69 USPQ 2D 1886, wherein the

court states "The same is not necessarily true in the chemical arts more generally. Even with the three-dimensional structures of enzymes such as COX-1 and COX-2 in hand, it may even now not be within the ordinary skill in the art to predict what compounds might bind to and inhibit them, …" Therefore, search of all the macrocyclic lactone suitable for the claimed method would require an undue experimentation.

17. In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). The cited references as a whole would have fairly suggested the claimed invention, particularly, Choi et al. and Tamura et al. teach that PKC activators with distinct structures are similarly useful for treating CNS disorders, and Alzheimer's disease in particular. Zhang et al. teaches that bryostatin 1 is a PKC activator. And Driedger et al. particularly teach macrocyclic lactones related to bryostatin are particularly useful for treating Alzheimer's disease. Considering the cited references as a whole, the employment of one particular bryostatin for treatment of Alzheimer's diseases would have been obvious as PKC activators in general, and PKC activators with bryostatin related macrocyclic lactone structure in particular, are known to be useful for treating Alzheimer's disease.

18. The examiner fully agrees that unrelated compounds are unpredictable. However, the cited references have fairly suggested the usefulness of bryostatin for treatment of Alzheimer's disease.

In response to applicant's argument that the cited references do not teach or suggest the effects on soluble beta-amyloid, the fact that applicant has recognized another advantage which would flow

naturally from following the suggestion of the prior art cannot be the basis for patentability when the differences would otherwise be obvious. See *Ex parte Obiaya*, 227 USPQ 58, 60 (Bd. Pat. App. & Inter. 1985). Furthermore, "In determining whether the subject matter of a patent claim is obvious, neither the particular motivation nor the avowed purpose of the patentee controls. What matters is the objective reach of the claim. If the claim extends to what is obvious, it is invalid under § 103." See KSR Int'l Co. v. TeleflexInc., 127 S.Ct. 1727, 1741-42 (2007)

19. The cited references as whole have fairly suggested that PKC activators, including bryostatin type macrocyclic lactone, are useful for treatment of Alzheimer's disease.

20. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

21. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Shengjun Wang whose telephone number is (571) 272-0632. The examiner can normally be reached on Monday to Friday from 7:00 am to 3:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreeni Padmanabhan, can be reached on (571) 272-0629. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/Shengjun Wang/
Primary Examiner, Art Unit 1627

22.